King Saud University
College of Sciences
Biochemistry Department

الأيض (١)
Metabolism (1)
BCH 340

Lecture 14: Ketone bodies

Intended learning outcomes (ILOs)

By the end of this lecture, students will be able to:

- Define ketone bodies and describe their physiological significance in energy metabolism.
- Explain the process of ketogenesis, including the tissues and conditions under which it occurs.
- Discuss the metabolic fates of ketone bodies in various tissues, including the heart, brain, and skeletal muscle.

Ketone bodies

- Ketone bodies, also known as ketones, are molecules produced by the liver from fatty acids during periods of:
  - Low food intake (fasting)
  - Carbohydrate restriction
  - Prolonged exercise
  - Untreated diabetes

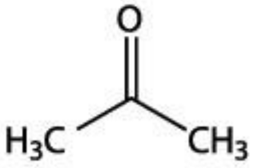
- They serve as an alternative energy source for the body (particularly the brain) when glucose availability is limited.
  - Normal physiological responses to carbohydrate shortages cause the liver to increase the production of ketone bodies from the acetyl-CoA generated from fatty acid oxidation.

Metabolism of ketone bodies

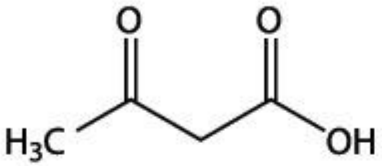
Production:

- Ketone bodies are synthesized primarily in the liver from acetyl-CoA, which is derived from the breakdown of fatty acids.

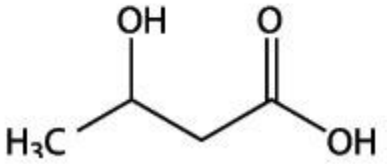
- The three main ketone bodies produced are:
  - Acetoacetate
  - β-hydroxybutyrate
  - Acetone



Acetone



Acetoacetate



2-Hydroxybutyric acid

Metabolism of ketone bodies (cont.)

Transport:

- Once produced, ketone bodies are released into the bloodstream.
    - Unlike fatty acids, ketone bodies are water-soluble, allowing them to be transported in the blood to tissues that can utilize them for energy.

Uptake by tissues:

- Ketone bodies are taken up by tissues such as the brain, heart, and skeletal muscles.
- In the brain, ketone bodies can cross the blood-brain barrier and serve as an important energy source during periods of glucose scarcity, such as fasting or prolonged exercise.

Metabolism of ketone bodies (cont.)

Conversion back to acetyl-CoA:

- Once inside cells, ketone bodies can be converted back to acetyl-CoA, which enters the TCA cycle to generate ATP.
  - Acetyl-CoA undergoes oxidation to produce NADH and FADH2, which then donate electrons to the electron transport chain, ultimately leading to the production of ATP through oxidative phosphorylation.

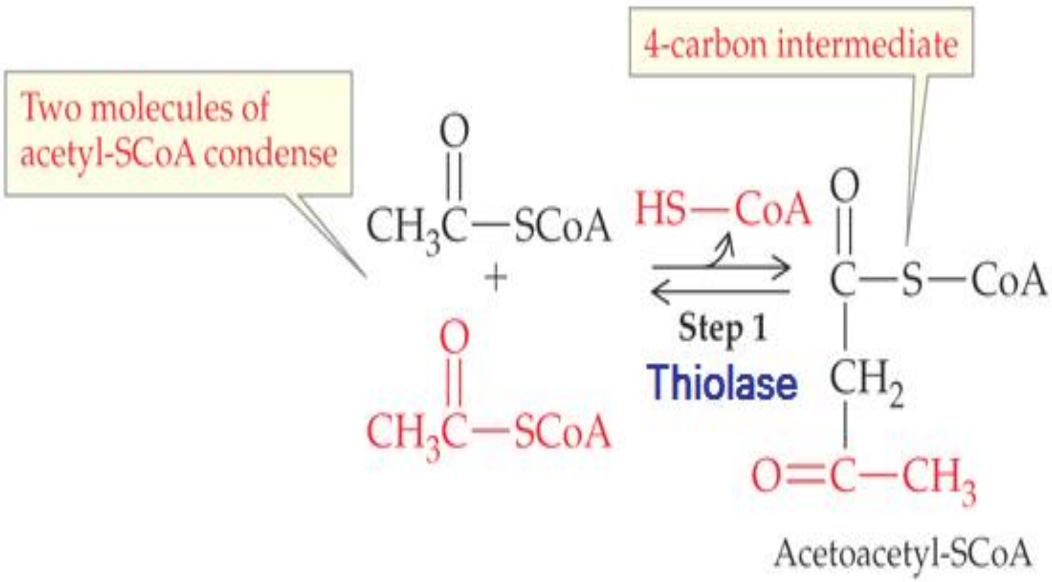
Ketogenesis

- In the absence of sufficient glucose, fatty acids from adipose tissue are transported to the liver. There, they undergo β-oxidation, resulting in the production of acetyl-CoA molecules.
- Excess acetyl-CoA produced from the breakdown of fatty acid cannot enter the TCA cycle due to low oxaloacetate levels (which is primarily used for gluconeogenesis in this state).
  - Instead, acetyl-CoA undergoes ketogenesis in the liver mitochondria, leading to the formation of ketone bodies.

Steps of ketogenesis

Step 1:

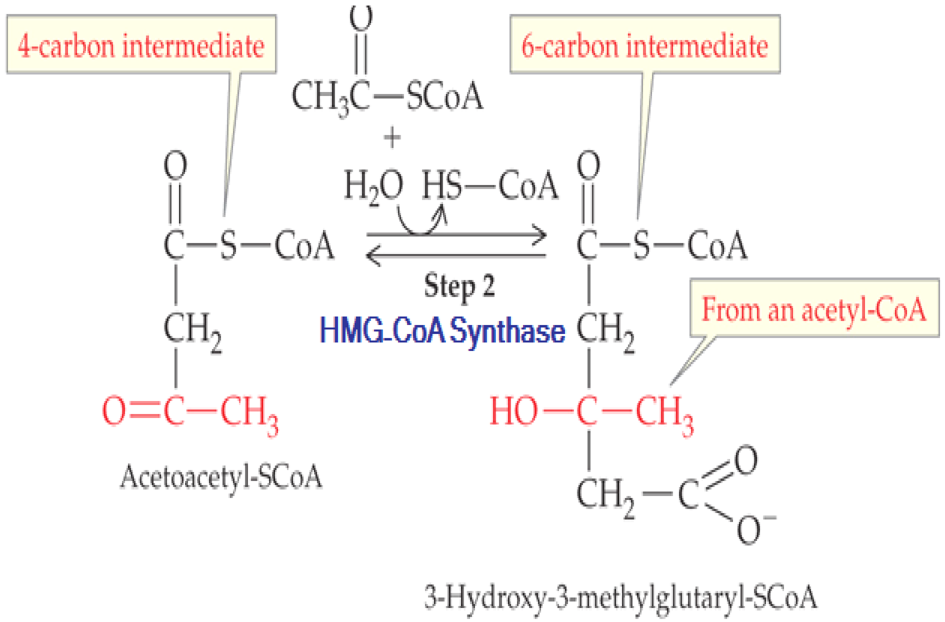
- Two molecules of acetyl-CoA (derived from the breakdown of fatty acids in β-oxidation) are combined to form acetoacetyl-CoA by the enzyme thiolase.



Steps of ketogenesis (cont.)

Step 2:

- In this step, a third molecule of acetyl-CoA interacts with acetoacetyl-CoA to produce β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) in a reaction catalyzed by HMG-CoA synthase.

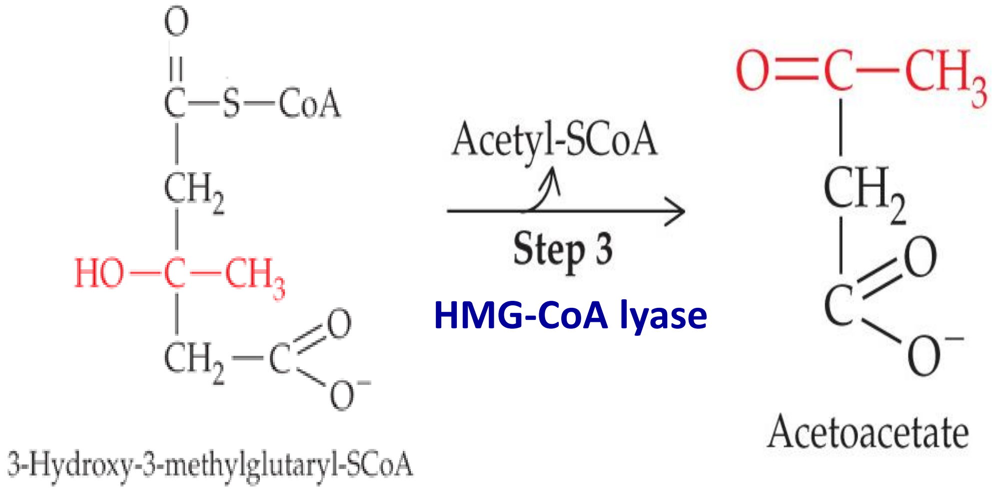


Steps of ketogenesis (cont.)

Step 3:

- β-hydroxy-β-methylglutaryl-CoA lyase catalyzes the cleavage of HMG-CoA, removing one molecule of acetyl-CoA.

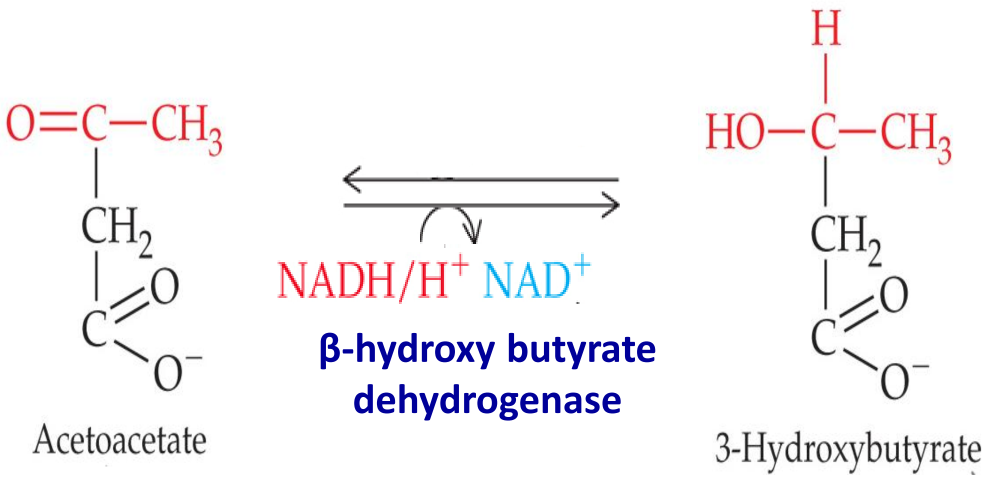
- This results in the production of the first of the ketone bodies (acetoacetate), which is the precursor of the other two ketone bodies produced by ketogenesis (β-hydroxybutyrate and acetone).



Steps of ketogenesis (cont.)

Step 4:

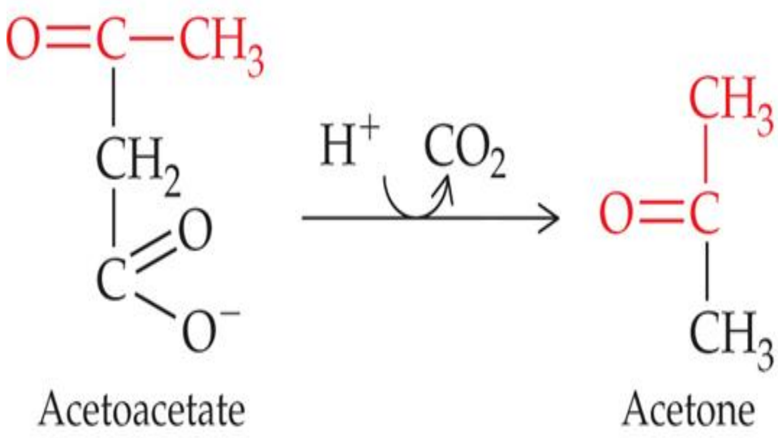
- The acetoacetate produced in the previous step reduced to β-hydroxybutyrate by β-hydroxy butyrate dehydrogenase.
- β-hydroxybutyrate and acetoacetate are linked through a reversible NADH-dependent reaction.



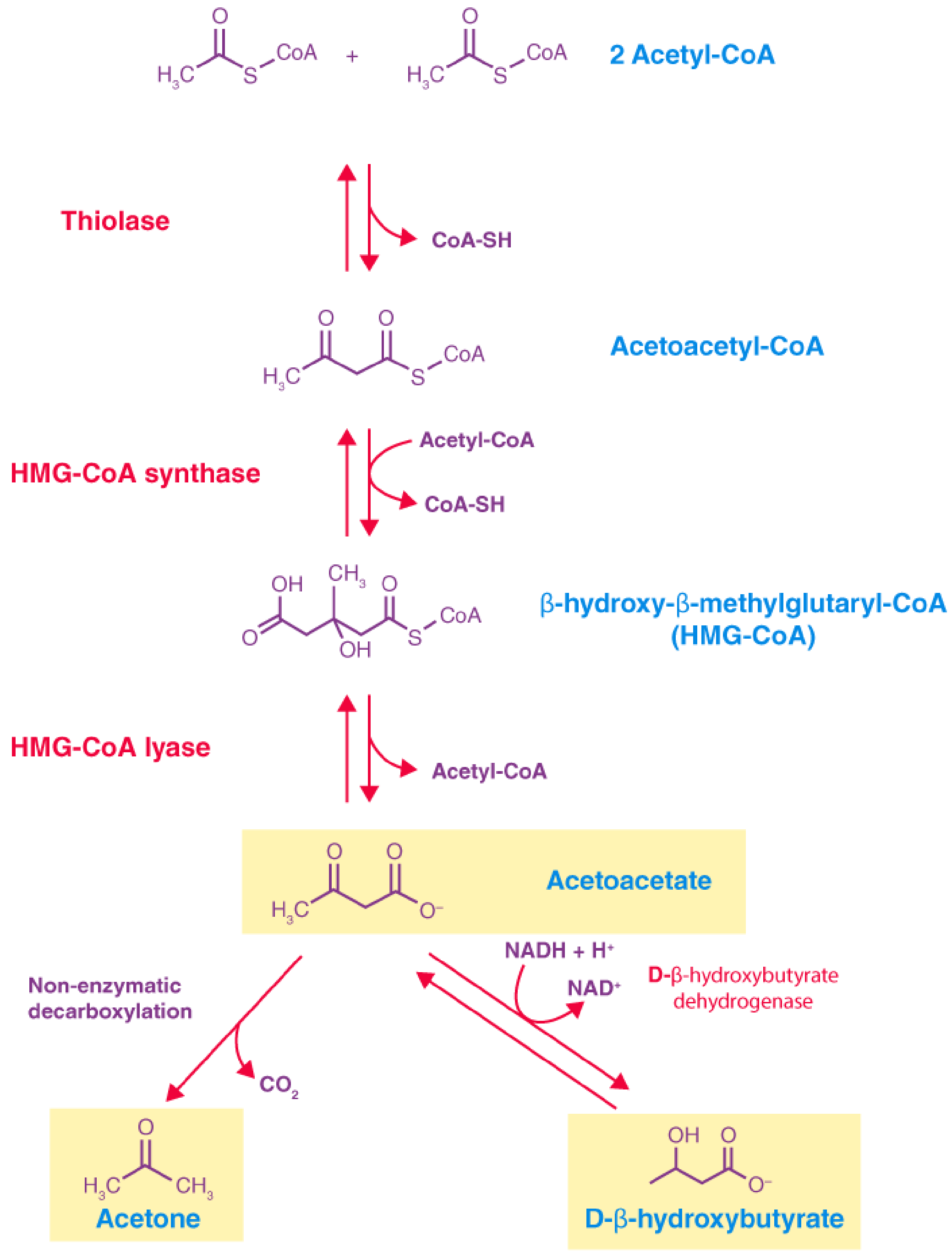
Steps of ketogenesis (cont.)

Step 5:

- Acetone is formed spontaneously as a byproduct when a small quantity of acetoacetate undergoes non-enzymatic decarboxylation in the bloodstream.
- It is primarily eliminated through exhalation because it is volatile. A smaller amount is excreted in urine and sweat.
- Acetone can be metabolized in the liver to produce acetate, which can then enter normal metabolic pathways and be converted ultimately into carbon dioxide and water.



Steps of ketogenesis



Ketosis

- Ketosis is a metabolic state characterized by elevated levels of ketone bodies in the blood. This typically occurs when the rate of ketone bodies production in the body is greater than the rate of their utilization.

- It's a normal physiological response, often seen during fasting, prolonged exercise, or when following a low-carbohydrate, high-fat diet like the ketogenic diet.

- Ketosis can also occur in diabetes, when the body does not have enough insulin to use glucose for energy.
  - In diabetes, ketosis is identified by the smell of acetone (a highly volatile ketone) on the patient's breath, along with the presence of ketone bodies in both urine (ketonuria) and blood (ketonemia).

Ketoacidosis

- Ketoacidosis is a serious medical condition that occurs when the body produces dangerously high levels of blood acids (ketone bodies).
- It's most commonly associated with uncontrolled diabetes, particularly type 1 diabetes, where the body doesn't produce enough insulin to properly regulate blood sugar levels.
- Symptoms of ketoacidosis include:
  - Excessive thirst
  - Frequent urination
  - Nausea, vomiting
  - Fruity-smelling breath
- If left untreated, ketoacidosis can lead to coma or even death.

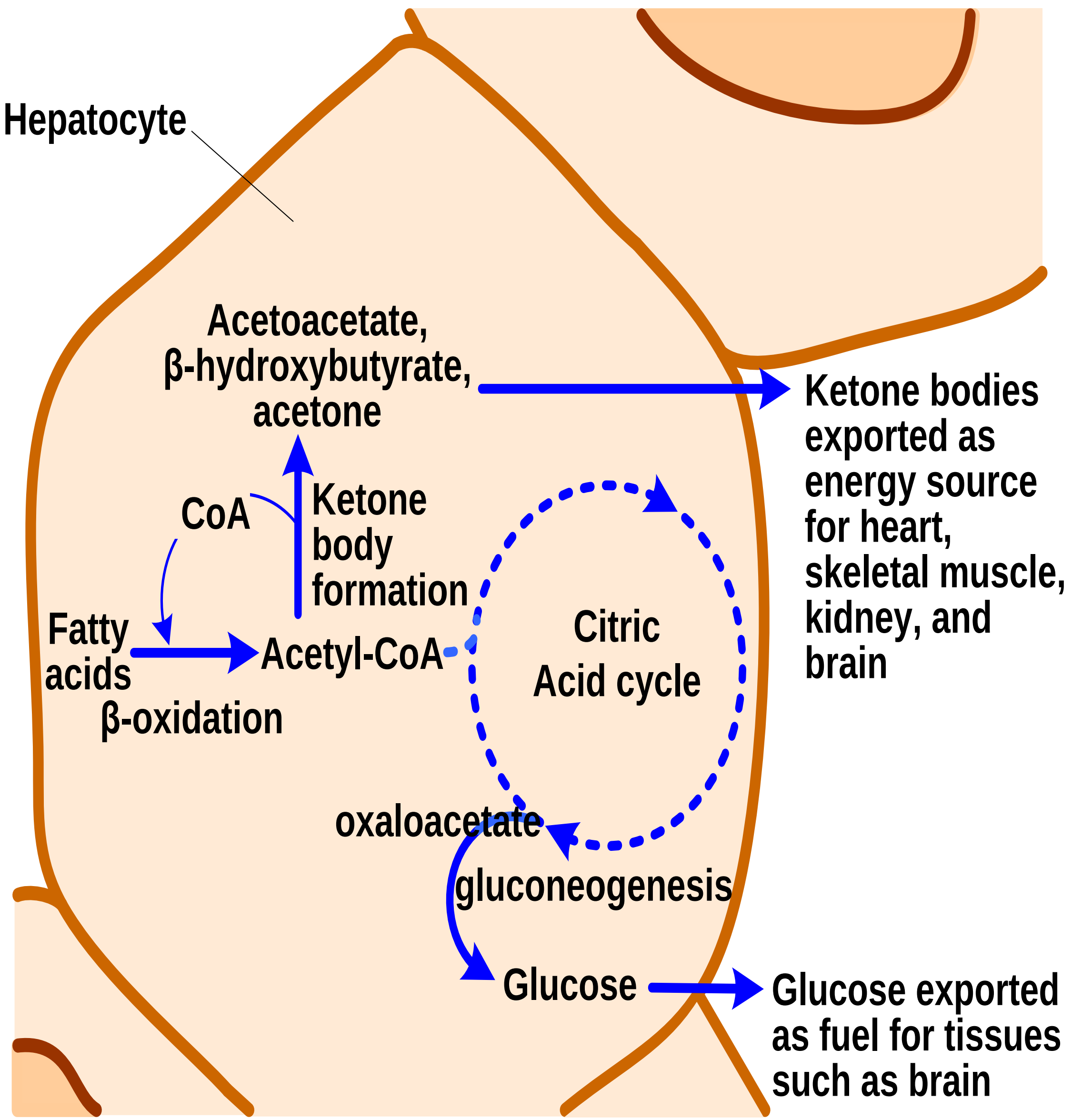
Utilization of ketone bodies (extrahepatic tissues)

- Ketone body utilization mainly occurs in extrahepatic tissues.
    - Although the liver is the primary site of ketone body production, it cannot use them for energy because it lacks the key enzymes required for ketolysis.

- β-hydroxybutyrate and acetoacetate are released into the bloodstream and transported from the liver to peripheral tissues, where they function as alternative energy source.

- Once taken up by cells, these ketone bodies are reconverted into acetyl-CoA, which then enters the TCA cycle to generate ATP.

Utilization of ketone bodies (extrahepatic tissues)



Utilization of ketone bodies (cont.)

In the well-fed, healthy conditions:

- Skeletal muscles typically derive only a small portion of their energy needs from ketone bodies, with most energy being supplied by glucose and fatty acids.

- The heart primarily uses fatty acids for energy, but it is metabolically flexible and can readily oxidize ketone bodies when their circulating levels increase (e.g., during fasting).
  - Under normal fed conditions, ketone bodies are not its major fuel source.

Utilization of ketone bodies (cont.)

Early stages of starvation:

- As the body enters starvation, liver glycogen becomes depleted, prompting a metabolic shift toward increased mobilization and oxidation of fat stores.
  - This results in an increase in hepatic ketone body production.

- During this phase, the heart and skeletal muscles increase their use of acetoacetate and other ketone bodies, helping to spare glucose so that more of it remains available for the brain.

Utilization of ketone bodies (cont.)

Prolonged starvation:

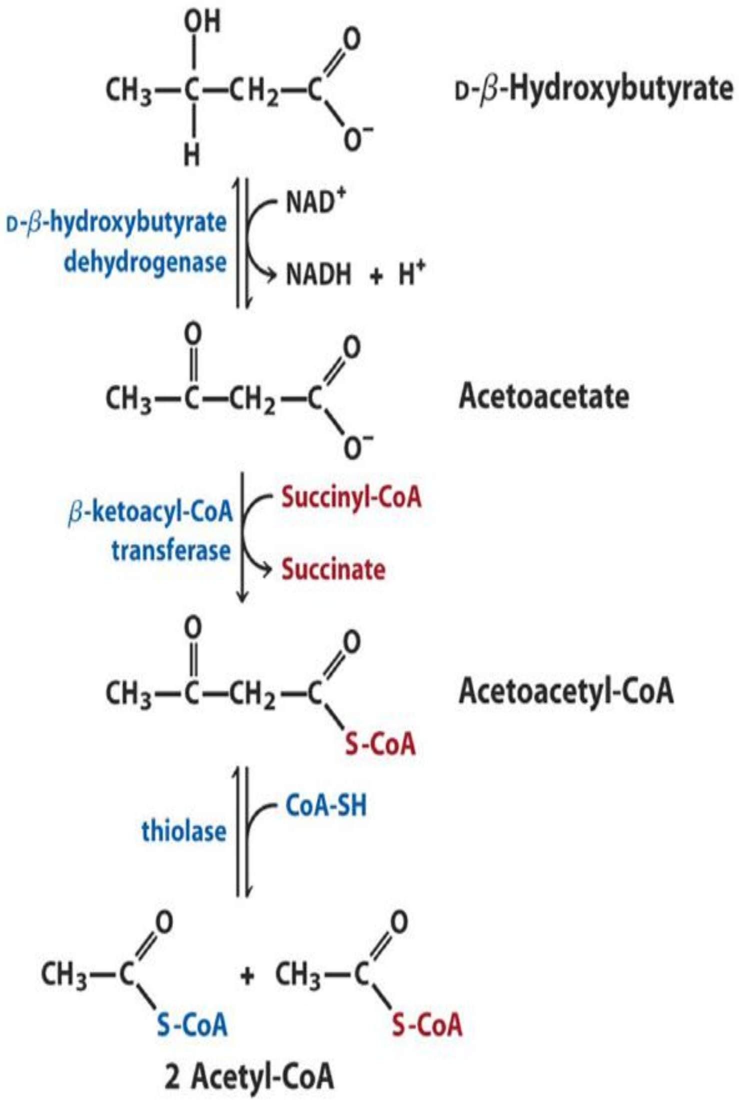
- With continued starvation, the body undergoes metabolic adaptations that increasingly favor the use of ketone bodies for energy.
- This shift is especially important for the brain, which gradually begins to utilize ketone bodies as a major fuel source, thereby reducing its dependence on glucose.
- During this stage, the brain can obtain up to 75% of its energy from ketone bodies, allowing glucose to be conserved for tissues that are unable to efficiently use ketone bodies.

Ketolysis

- Ketolysis is the metabolic process by which ketone bodies are broken down and used for energy within cells. This process takes place primarily in the mitochondria of extrahepatic tissues.

- Within the mitochondria, ketone bodies are converted into acetyl-CoA through the following steps:

  1. β-hydroxybutyrate is oxidized to acetoacetate by the enzyme β-hydroxybutyrate dehyrogenase.

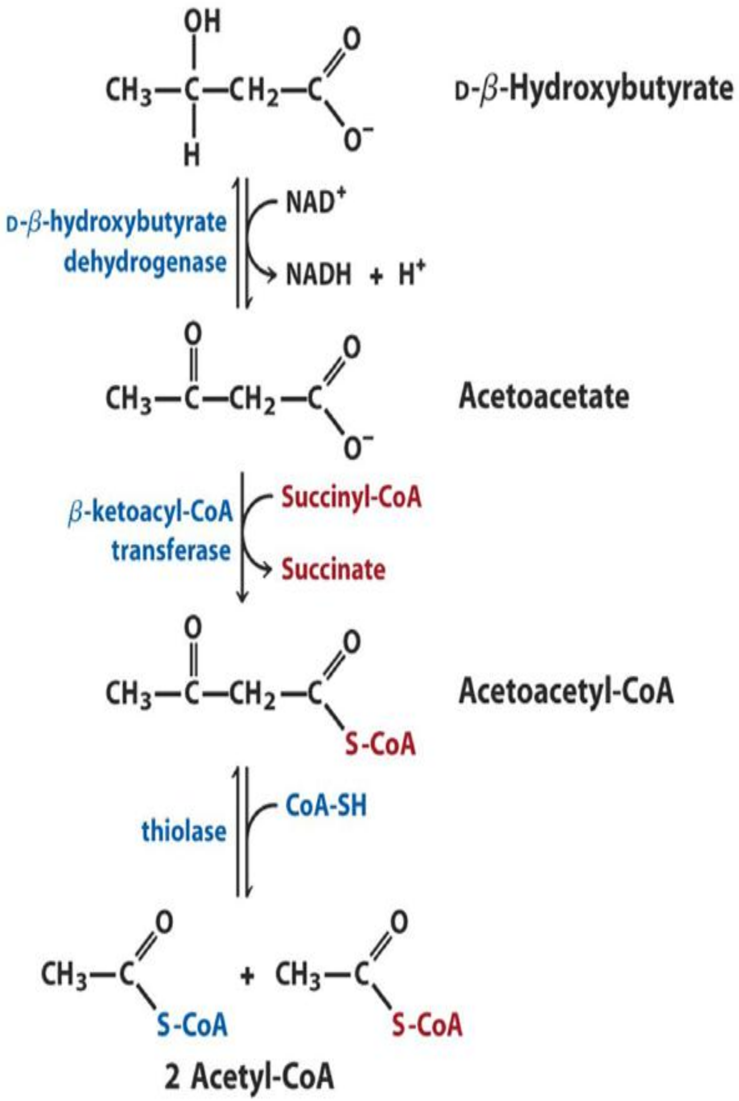


Ketolysis (cont.)

2. Acetoacetate is then activated to acetoacetyl-CoA by β-ketoacyl-CoA transferase. This enzyme found in non-hepatic tissues and uses succinyl-CoA as the CoA donor.

3. Acetoacetyl-CoA is cleaved by thiolase into two molecules of acetyl-CoA, which then enter the TCA cycle for ATP production.

How many molecules of ATP are generated by the oxidation of two molecules of acetyl-CoA?



Summary

- Ketone bodies are water-soluble molecules produced by the liver serving as alternative energy sources, particularly for the brain and muscles. The main types include acetoacetate, β-hydroxybutyrate, and acetone.

- Ketogenesis is the process through which the liver synthesizes ketone bodies, such as acetoacetate and β-hydroxybutyrate, from fatty acids during conditions like fasting or low carbohydrate intake.

- Ketolysis is the breakdown of ketone bodies into acetyl-CoA for energy production. This occurs mainly in extrahepatic tissues, such as muscle and brain, during times of increased energy demand or when glucose availability is limited.